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RESEARCH ARTICLE

Thirty Years of Orphan Drug Legislation and the Development of Drugs to Treat Rare Seizure Conditions: A Cross Sectional Analysis

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Abstract

Background

Epilepsy is a serious chronic health condition with a high morbidity impairing the life of patients and afflicted families. Many epileptic conditions, especially those affecting children, are rare disorders generating an urgent medical need for more efficacious therapy options. Therefore, we assessed the output of the US and European orphan drug legislations.

Methods

Quantitative analysis of the FDA and EMA databases for orphan drug designations according to STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) criteria.

Results

Within the US Orphan Drug Act 40 designations were granted delivering nine approvals, i.e. clobazam, diazepam viscous solution for rectal administration, felbamate, fosphenytoin, lamotrigine, repository corticotropin, rufinamide, topiramate, and vigabatrin. Since 2000 the EMA granted six orphan drug designations whereof two compounds were approved, i.e. rufinamide and stiripentol. In the US, two orphan drug designations were withdrawn. Orphan drugs were approved for conditions including Lennox-Gastaut syndrome, infantile spasms, Dravet syndrome, and status epilepticus. Comparing time to approval for rufinamide, which was approved in the US and the EU to treat rare seizure conditions, the process seems faster in the EU (2.2 years) than in the US (4.3 years).

Conclusion

Orphan drug development in the US and in the EU delivered only few molecular entities to treat rare seizure disorders. The development programs focused on already approved

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Abbreviations: FDA, Food and Drug Administration; EMA, European Medicines Agency.

antiepileptic drugs or alternative pharmaceutical formulations. Most orphan drugs approved in the US are not approved in the EU to treat rare seizures although some were introduced after 2000 when the EU adopted the Orphan Drug Regulation.

Introduction

Epilepsy is a serious chronic health condition with a high morbidity impairing the life of patients and affected families through seizures, hospitalizations, emergency department visits, and medication burden [1, 2]. Particularly, seizure onset in childhood can compromise the child's development and frequently causes lifelong disability and dependency [2]. Epilepsy comprises a large group of syndromes whereof some meet the criteria for a rare disease according to the World Health Organization (WHO), i.e. a condition affecting less than 65–100 in 100,000 inhabitants [3]. For example, Lennox-Gastaut syndrome with an estimated prevalence of 15/100,000, West syndrome (infantile spasms) with an estimated prevalence of 8/100,000, Dravet syndrome (severe myoclonic epilepsy in infancy) with an estimated birth-prevalence of 2.5/100,000, or Pyridoxine-dependent epilepsy with 0,2/100,000 fulfill the WHO definition of a rare disease [4]. Today clinically available anti-epileptic drugs can control seizures in approximately two-third of patients [5–7], particularly in rare seizure conditions such as Lennox-Gastaut or Dravet syndrome long term prognosis is guarded and most patients are refractory to medical treatment [8, 9]. Psychomotor delay and neuropsychiatric symptoms occur regularly. In addition, most often anti-epileptic pharmacotherapy is limited by drug-drug interactions, adverse drug events, and complex dose regimens impairing adherence [10–13].

Since 1983, the US Orphan Drug Act has stimulated the development of orphan drugs by granting various incentives, such as seven years marketing exclusivity, tax credit for 50% of clinical trial costs, protocol assistance, Food and Drug Administration (FDA) fee waiver, and orphan products grant programs [14]. A compound qualifies for the incentives described in the US Orphan Drug Act when a disease affects less than 200,000 patients in the US or when economic viability is lacking although prevalence exceeds 200,000 [3]. In 1999, the European Medicines Agency (EMA) adopted the legislation for orphan drugs (Regulation (EC) No 141/2000), which came into force in 2000, to stimulate orphan drug development in the European Union (EU) by granting, for example, up to ten years marketing exclusivity after approval (plus two years for orphan drugs with a pediatric investigation plan), fee reduction, and protocol assistance [15]. In the EU, a compound qualifies for orphan drug designation when it is indicated for a life-threatening or chronically debilitating condition affecting less than five in 10,000 persons or when it is improbable to sufficiently generate return of investment although a life-threatening, seriously debilitating or serious and chronic condition affects more than five in 10,000 patients [16]. A furtherprerequisite is absence of a satisfactory method of diagnosis, prevention, or treatment, or if it exists, the new medicinal product must be of significant benefit to the patients [16].

During the last decades scientists, policy makers, and pharmaceutical companies have advocated to respond to challenges in orphan drug development. In addition, political and legislative developments, such as the US Orphan Drug Act and the Orphan Drug Regulation in the EU, have changed the environment in orphan drug development. Considering the unmet medical need for anti-epileptic treatments, drug development in orphan epilepsy—as in any rare disease—is challenged by small sample sizes, heterogeneous pathomechanisms, and involvement of children. Therefore, we systematically analyzed the impact of the US Orphan Drug Act

and the Orphan Drug Regulation in the EU on orphan drug development in rare seizure conditions by investigating orphan drug designations and approvals, time to approval, compounds and indications. In addition, we examined pivotal trial designs to illustrate quality indicators, such as randomization or control, in clinical research of approved orphan drugs to treat rare seizure conditions.

Methods

This cross-sectional analysis was conducted according to STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) criteria.

Data acquisition

In December 2015, we searched the FDA database "Search Orphan Drug Designations and Approvals" [17], the EMA databases "Rare disease (orphan) designations" [18], "European public assessment reports/orphan medicines" [19], and "Register of designated Orphan Medicinal Products" [20] for designated and approved orphan drugs to treat rare seizure conditions. First a semantic search was performed using search terms, such as seizure, epilepsy, status epilepticus, and spasm followed by a specific search for epilepsy syndromes based on the ILAE definition of electroclinical syndromes and other epilepsies [21]: West syndrome, Dravet syndrome, myoclonic encephalopathy, Panayiotopoulos syndrome, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, Otahara syndrome, and early myoclonic encephalopathy. Additionally, an inverse search for known and new substances for epilepsy and seizure treatment based on recent EILAT reports [22] and ATC code (N03A Antiepileptics) was added: brivaracetam, bumetanide, cannabidiol, cannabidivarin, carbamazepine, carisbamate, clobazam, clonazepam, diazepam, divalproex, eslicarbazepine, ethosuximide, ezogabine or retigabine, felbamate, fosphenytoin, gabapentin, ganaxolone, lacosamide, lamotrigine, levetiracetam, lorazepam, metharbital, oxcarbazepine, paramethadione, perampanel, phenacemide, phenobarbital, phenytoin, phensuximide, pregabalin, primidone, rufinamide, stiripentol, tiagabine, topiramate, trimethadione, valproic acid or valproate, vigabatrin, and zonisamide. The Orphanet Report series was consulted for epidemiological data on rare seizure conditions [4]. Information on design and endpoints of clinical trials was extracted from the drug label which was accessed by entering the respective drug name as search term at https://www.accessdata.fda.gov/scripts/cder/drugsatfda/ or from the European Public Assessment Reports (EPAR). JHD and AL independently performed the database search and extracted the information from the databases.

Definitions

Time to FDA approval or marketing authorization by the EMA and European Commission was defined as the time period from orphan drug designation until approval by the FDA or EMA and European Commission.

Statistical analysis

Data were summarized using techniques of descriptive statistics. As such, continuous variables were summarized with means and standard deviations, and categorical variables were summarized with frequencies and percentages. Statistical analyses were performed using SAS Enterprise Guide version 9.1 (SAS, Cary, NC, USA). Data from the FDA and EMA were analyzed both separately and comparatively. Missing data were not imputed and sensitivity analysis was not performed.

Results

Designations and approvals

The FDA granted 40 orphan drug designations for treatment of rare seizure conditions resulting in nine approvals representing an acceptance rate of 23% (Fig 1). Two designations, i.e. Pr-122 (redox-phenytoin) and Pr-320 (molecusol-carbamazepine), were withdrawn. Reasons for non-approval were not publicly available. In the EU, six compounds received a positive opinion by the EMA's Committee on Orphan Medicines (COMP) and were designated as orphan drugs (Fig 1). Midazolam hydrochloride for oromucosal use for the treatment of seizures which continue for at least five minutes received a negative opinion. The European Commission granted a central marketing authorization for two compounds to treat rare seizure conditions, i.e. rufinamide and stiripentol, representing an acceptance rate of 33%. Only rufinamide was designated and approved to treat Lennox-Gastaut syndrome in the US and in the EU. Eight compounds that were approved in the US for treatment of rare seizure conditions and epilepsy syndromes were not submitted for orphan drug designation in the EU, i.e. clobazam, diazepam viscous solution for rectal administration, felbamate, fosphenytoin, lamotrigine, repository corticotropin or adrenocorticotropic hormone, topiramate, and vigabatrin. Three of these compounds (i.e. clobazam, repository corticotropin or adrenocorticotropic hormone, and vigabatrin) were designated and approved in the US after the year 2000 when the Orphan Drug Regulation was already introduced in the EU. In total, 20 designations were obtained in the US after the Orphan Drug Regulation was introduced in 2000 in the EU, while these designations were not obtained in the EU. Two compounds, i.e. fosphenytoin and repository corticotropin or adrenocorticotropic hormone, were first approved within the US Orphan Drug Act (Fig 1).

Until December 2015, the US Orphan Drug Act has delivered 500 approved orphan drugs in total, while in the EU 103 orphan drugs have received marketing authorization since 2000.

Time to approval

Mean time to approval for orphan drugs for treating rare seizure conditions was 5.7 years (standard deviation ± 2.0 years, range 3 to 8.8 years) in the US and in the EU 2.2 years for rufinamide and 5.1 years for stiripentol (Fig 2). For rufinamide, a compound that was approved in the US and the EU for the same indication, time to approval was 4.3 years in the US and 2.2 years in the EU.

Compounds and indications

Cannabidiol obtained most designations (FDA N = 6 and EMA N = 1) (Table 1). Cannabidiol obtained two orphan drug designations by the FDA for treatment of Dravet syndrome (time difference between designations was 2 months) and two orphan drug designations for treatment of Lennox-Gastaut syndrome (time difference between designations was 4 months) (Table 1). Designations within the same conditions were granted by different companies. Designations were most frequently granted for treatment of Lennox-Gastaut syndrome (FDA N = 8 and EMA N = 1), infantile spasms (West syndrome) (FDA N = 7 and EMA N = 1), and Dravet syndrome (severe myoclonic epilepsy in infancy) (FDA N = 4 and EMA N = 3) (Table 1). Orphan drugs were approved for conditions including Lennox-Gastaut syndrome, infantile spasms, Dravet syndrome, and status epilepticus. Most compounds were approved for treatment of Lennox-Gastaut (FDA N = 5 and EMA N = 1) (Table 1). Compounds designated in the US and the EU obtained orphan drug designation for the same indication. Rufinamide was approved in the US and in the EU for treatment of Lennox-Gastaut syndrome. Seven FDA

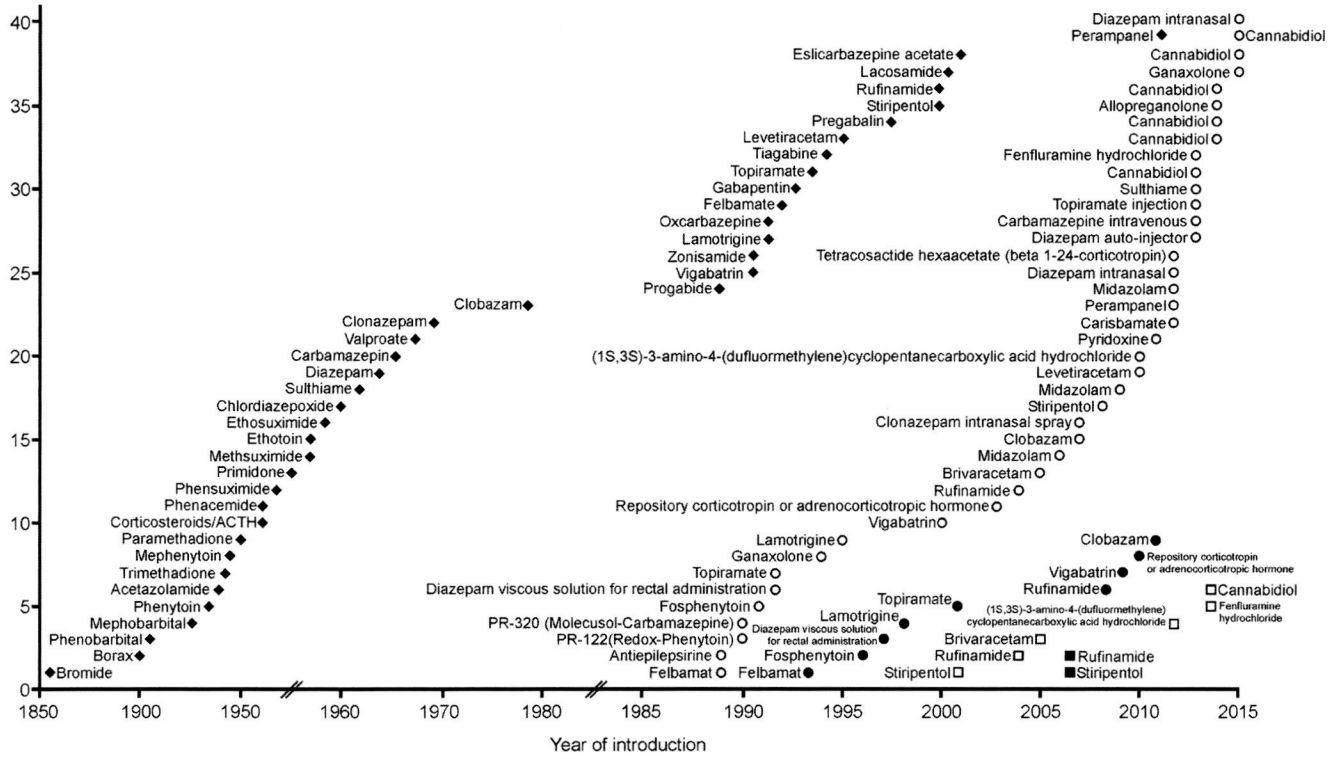

Fig 1. Cumulative number of approved non-orphan antiepileptic drugs (◆) illustrating the year of first licensing or the first mention of clinical use in a country of Europe, the United States, or Japan (adapted from [31]). Cumulative number of US orphan drug designations (○) and approvals (●). Cumulative number of orphan drug designations (□) and approvals (■) in the EU.

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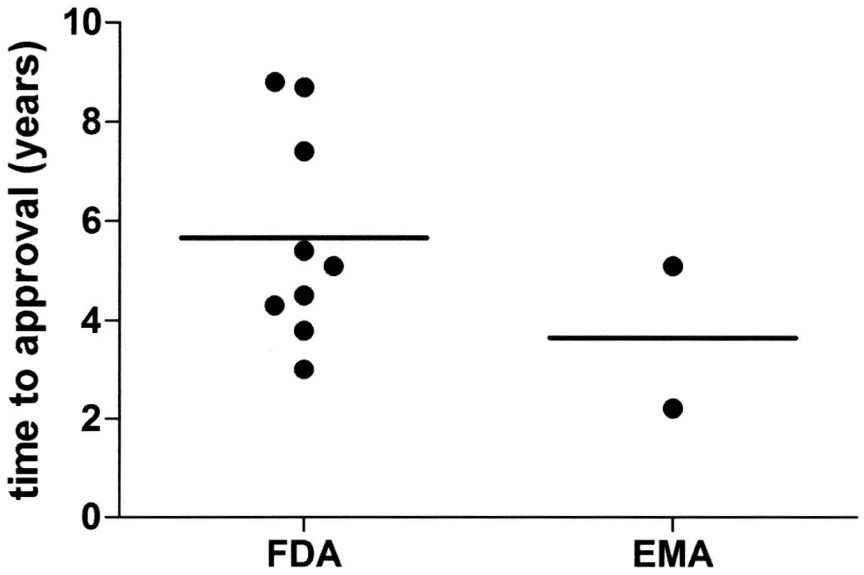

Fig 2. Time to approval of compounds intended to treat orphan epileptic conditions. Lines indicate means.

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